Acknowledgements

Firstly, I would like to thank my mentor, Dr. Louis M. Pelus, who has provided me with support and guidance throughout my education in his laboratory. He gave me freedom to develop my own project and experiments but was always present to give encouragement, ideas, and advice.

I am grateful for my fellow lab members, past and present, Dr. Pratibha Singh, Dr. Jennifer Speth, and Dr. Jonathan Hoggatt. All were readily available and willing to offer their thoughts and suggestions or to lend a helping hand with an extensive experiment.

I thank my committee members, Dr. Hal E. Broxmeyer, Dr. Edward F. Srour, and Dr. Melissa A. Kacena, who provided me with guidance and recommendations throughout my work on this thesis project. I would also like to thank Dr. Christie Orschell for her assistance with some of the radiation studies and her presence as an advising resource.

Lastly, I would like to thank my family and friends. They never failed to demonstrate their faith in my abilities and offer their unwavering support throughout my time in graduate school.

Kayla N. Stilger

PROSTAGLANDIN E_2 PROMOTES RECOVERY OF HEMATOPOIETIC STEM AND PROGENITOR CELLS AFTER RADIATION EXPOSURE

The hematopoietic system is highly proliferative, making hematopoietic stem and progenitor cells (HSPC) sensitive to radiation damage. Total body irradiation and chemotherapy, as well as the risk of radiation accident, create a need for countermeasures that promote recovery of hematopoiesis. Substantive damage to the bone marrow from radiation exposure results in the hematopoietic syndrome of the acute radiation syndrome (HS-ARS), which includes life-threatening neutropenia, lymphocytopenia, thrombocytopenia, and possible death due to infection and/or hemorrhage. Given adequate time to recover, expand, and appropriately differentiate, bone marrow HSPC may overcome HS-ARS and restore homeostasis of the hematopoietic system. Prostaglandin E_2 (PGE_2) is known to have pleiotropic effects on hematopoiesis, inhibiting apoptosis and promoting self-renewal of hematopoietic stem cells (HSC), while inhibiting hematopoietic progenitor cell (HPC) proliferation. We assessed the radiomitigation potential of modulating PGE_2 signaling in a mouse model of HS-ARS. Treatment with the PGE_2 analog 16,16 dimethyl PGE_2 ($dmPGE_2$) at 24 hours post-irradiation resulted in increased survival of irradiated mice compared to vehicle control, with greater recovery in HPC number and colony-forming potential measured at 30 days post-irradiation. In a sublethal mouse model of irradiation, $dmPGE_2$-treatment at 24 hours post-irradiation is associated with enhanced recovery of HSPC populations

compared to vehicle-treated mice. Furthermore, $dmPGE_2$-treatment may also act to promote recovery of the HSC niche through enhancement of osteoblast-supporting megakaryocyte (MK) migration to the endosteal surface of bone. A 2-fold increase in MKs within 40 um of the endosteum of cortical bone was seen at 48 hours post-irradiation in mice treated with $dmPGE_2$ compared to mice treated with vehicle control. Treatment with the non-steroidal anti-inflammatory drug (NSAID) meloxicam abrogated this effect, suggesting an important role for PGE_2 signaling in MK migration. *In vitro* assays support this data, showing that treatment with $dmPGE_2$ increases MK expression of the chemokine receptor CXCR4 and enhances migration to its ligand SDF-1, which is produced by osteoblasts. Our results demonstrate the ability of $dmPGE_2$ to act as an effective radiomitigative agent, promoting recovery of HSPC number and enhancing migration of MKs to the endosteum where they play a valuable role in niche restoration.

Louis M. Pelus, Ph.D., Chair

Table of Contents

List of Figures

Chapter 1

Chapter 2

Chapter 3